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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/542,088	07/13/2005	Jurgen Braunger	26797U	1055

34375 7590 08/04/2009

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EXAMINER	
PAGONAKIS, ANNA	
ART UNIT	PAPER NUMBER
1614	
MAIL DATE	DELIVERY MODE
08/04/2009	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/542,088	BRAUNGER ET AL.	
	Examiner	Art Unit	
	ANNA PAGONAKIS	1614	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *04 June 2009*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *89-94* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *89-94* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office Action has been withdrawn pursuant to 37 CFR 1.114. Applicant's payment and submission filed 6/4/2009, has been received and entered into the present application. Accordingly, prosecution has been reopened.

Applicant is reminded of the election of species of roflumilast and all trans-retinoic acid in the reply filed 2/28/2008 in response to the restriction requirement dated 2/7/2008.

Applicant's arguments, filed 6/4/2009 have been fully considered. Rejections not reiterated from previous Office Actions are hereby withdrawn. The following rejections are either reiterated or newly applied. They constitute the complete set of rejections presently being applied to the instant application.

Claims 89-94 are currently under examination and the subject of this Office Action.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner

to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claims 89-94 rejected under 35 U.S.C. 103(a) as being unpatentable over Benoit et al. (U.S. 6,624,154) and Reid (Current Opinion in Investigational Drugs, provided by Applicant) and Sacchi et al. (Hematological 1997; 82: 106-121), in light of Zhao (Journal of Pharmacology and Experimental Therapeutics, 2003, vol. 205, no. 2 pages 565-572) and in light of Remington's Pharmaceutical Science (pages 420-425, 1980).

Benoit et al teach the treatment of leukemia with the administration of rolipram (see claims 1, 4 and 13).

Zhao et al teach that rolipram is in fact a phosphodiesterase 4 inhibitor (see title).

Benoit et al. does not teach the use of roflumilast as the PDE type 4 inhibitor, nor does it teach the use of all trans retinoic acid as a differentiation inducing agent.

Reid teaches that roflumilast is a nonselective PDE4 inhibitor which appears to be the major PDE isoenzyme involved in the regulation of cAMP-mediated functions in airway inflammatory and structural cells (introduction). Roflumilast is substantially more potent than rolipram (page 1165, synthesis and SAR, last 3 lines) and inhibit the functions of both immunocompetent and inflammatory cells to a greater level than rolipram (page 1168, second column, last paragraph).

Redi does not teach the use of roflumilast for the treatment of myeloid leukemia, not does it teach all trans retinoic acid as the differentiation inducing agent.

Sacchi et al teach that there is considerable evidence that retinoids have a potent antiproliferative effect, and may be effective in the treatment of a variety of human diseases including cancer (page 107, column 1, first 4 lines), further ATRA (all trans retinoic acid) has proven active against a range of malignancies in isolated tissue culture systems and in human clinical trials (page 109, column 1, under Metabolism). The therapeutic use of ATRA in acute promyelocytic leukemia (APL) was pioneered in the

late eighties with results of 94 percent complete remissions (CR) using ATRA alone, generating tremendous interest in the clinical use of ATRA in APL (page 111, column 2, paragraph 3). Retinoids seem to have a preferential effect on patients with mature T-cell lymphoma. L-ATRA renders B-cell lymphoma lines more susceptible to apoptosis by down-regulating bcl-2 gene expression suggesting that L-ATRA might be also useful for treating B-cell non-Hodgkin's lymphoma (page 115, column 1, first paragraph). In vitro ATRA can inhibit proliferation of myeloma cells by the downregulation of IL-6 receptors and/or its signal transducer glycoprotein 130 (gp130) surface expression on neoplastic cells, and by inhibition of IL-6 production by myelomatous and stromal cells (page 115, column 1, under ATRA in multiple myeloma). Expanding the spectrum of hematological malignancies, that may respond to ATRA remains a challenge, but several results show some activity of retinoids alone or in combination with other drugs in juvenile chronic myelogenous leukemia, myelodysplastic syndrome, cutaneous T-cell lymphoma and chronic myelogenous leukemia. Studies exploring the potential clinical synergim of ATRA-based combination therapies (e.g., with growth factors, other differentiating agents such as vitamin D3, immunomodulators like interferons or chemotherapeutic agents appear to be especially interesting (page 116, last paragraph).

The differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains because Benoit et al. broadly teaches the use of a PDE 4 inhibitor, rolipram, for the treatment of a lymphoid malignancy. Although, roflumilast is not specifically disclosed by the reference, Reid teaches that that roflumilast is a PDE 4 inhibitor, which as described is more potent that rolipram. Further, Sacchi teaches the treatment of ATRA for various lymphoid malignancies.

Considering the teachings of Benoit et al. who discloses the use of a PDE4 inhibitor for the treatment of a lymphoid malignancy, and also considering that it is well known in the art that roflumilast

is a PDE4 inhibitor, but also that it is more potent than roflumilast and that additionally ATRA is used for the treatment of various lymphoid malignancies, it would have been obvious to one of ordinary skill in the art to use roflumilast as the PDE4 inhibitor for the treatment of myeloid leukemia. Such a person would have been motivated to employ such roflumilast with a reasonable expectation to provide the same or similar therapeutic effects as rolipram disclosed by Reid and, further, because it is more potent than rolipram.

Further, one would have been motivated to additionally administer ATRA since it is also well known for the treatment of lymphoid malignancies. One of ordinary skill in the art would have been motivated to combine the teachings above since as combined would teach the invention as claimed. The idea of combining the administration of an agent known to be useful in the treatment of lymphoid malignancies flows logically from having been taught in the prior art.

The use of pharmaceutically acceptable salts of the elected compound would have been a matter well within the purview of the skilled artisan. As taught by Remington's Pharmaceutical Sciences, drugs may be formulated into salts to modify the duration of action of a drug; to modify the transportation and distribution of the drug in the body; to reduce toxicity; and to overcome difficulties encountered in pharmaceutical formulation procedures or in the dosage form itself (see column 2 of page 424, first paragraph). Thus, it would have been obvious to the skilled artisan motivated by any one or more of these factors to formulate the active agent into a pharmaceutically acceptable salt to enhance the pharmacokinetic parameters of the drug or to reduce the toxicity with the reasonable expectation that the therapeutic benefit of the agent in salt form would have been the same or substantially similar to that of the agent itself.

Conclusion

No claim is found to be allowable.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to ANNA PAGONAKIS whose telephone number is (571)270-3505. The examiner can normally be reached on Monday thru Thursday, 9am to 5pm EST.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Ardin H. Marschel can be reached on 571-272-0718. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

AP

/Ardin Marschel/
Supervisory Patent Examiner, Art Unit 1614